I-10
REGULATION OF INFLAMMATION BY ENDOGENOUS DANGER SIGNALS IN TISSUE INJURY AND ARTHRITIS

A.M. Piccinini. *Kennedy Inst. of Rheumatology, Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal Sci., Univ. of Oxford, Oxford, United Kingdom*

Inflammation is now recognized as an important component of the pathophysiology of a number of diseases that were historically regarded as non-inflammatory, including atherosclerosis, osteoarthritis, cancer and metabolic disorders like type 2 diabetes. In these conditions, inflammation occurs in the absence of any pathogen and is therefore defined as sterile inflammation. This raises the question: what are the inciting sterile stimuli and the host receptors that mediate this inflammatory response? During recent years, it has become increasingly accepted that the immune system is designed to combat danger posed by both infection and injury, rather than to merely recognize non-self. Evolutionarily conserved pattern recognition receptors (PRRs) sense danger signals generated upon infection (pathogen-associated molecular patterns - PAMPs) and endogenous molecules created upon tissue injury (damage-associated molecular patterns - DAMPs) and, in response, activate inflammatory signalling pathways. DAMPs include intracellular molecules released from necrotic cells, extracellular matrix (ECM) fragments and ECM molecules upregulated upon injury. DAMPs are vital for tissue repair, however, compelling evidence from both human studies and experimental animal models suggests that DAMPs are also implicated in inflammatory diseases such as rheumatoid arthritis. Here, in an attempt to initiate repair, they induce the production of inflammatory mediators that trigger further tissue damage establishing a vicious cycle that contributes to the persistence of inflammation. This talk will discuss what is known about the molecular mechanisms by which this network of diverse endogenous danger signals, and their receptors, drives inflammation, discuss whether DAMPs also stimulate inflammation in osteoarthritis and ask if there is any interplay between endogenous danger signals and other inflammatory mediators. Here I will focus on the latest, at times controversial, developments in the understanding of these inflammatory pathways and highlight their relevance in arthritis.

I-11
THE INTERACTIONS OF OSTEOARTHRITIS WITH OTHER COMMON CONDITIONS

G.A. Hawker. *Univ. of Toronto, Toronto, ON, Canada*

World-wide, there has been an unprecedented rise in the number of persons living with obesity and well into old age, and thus with multiple chronic conditions. Among the most common conditions are diabetes mellitus (DM), cardiovascular disease (CVD), hypertension (HT), and osteoarthritis (OA), which commonly co-occur. Currently, it is estimated that as many as 90% of individuals aged 65+ years with OA are living with at least one other chronic condition. Although less well studied, the prevalence of OA in people with DM, CVD and HT also appears to be high. 'Arthritis' and painful hips/knees limiting activity, suggesting OA, have been reported in 50-60% of people with heart disease or DM. The confluence of these conditions in obese patients with knee OA has led to the concept of 'metabolic OA' and to studies examining both the role of inflammatory adiopokines in the pathogenesis of OA, as well as the impact of OA on outcomes of these other common chronic conditions. This presentation will highlight key findings and future directions for this research.

I-12
TOWARDS BETTER ANIMAL MODELS OF OA PAIN WITH HIGHER TRANSLATIONAL VALUE

J.J. McDougall. *Dalhousie Univ., Halifax, NS, Canada*

Purpose: The primary concern of patients living with osteoarthritis (OA) is chronic intractable pain. Current drug therapies are only moderately effective in a subset of patients and long-term use of these drugs can be risky. Thus, there is an urgent need for new, efficacious analgesics which will provide pain relief for all OA patients. One of the main hurdles in developing novel therapeutics to treat OA pain is the clinical relevance of the animal models used to test the drugs. All OA models recapitulate only some of the features of the disease and each model has advantages and limitations. Furthermore, OA is not a homogeneous disease and the pain associated with the various types of OA can vary from patient to patient. Some forms of OA have a strong inflammatory component, for example, which may be managed by anti-inflammatories such as non-steroidal anti-inflammatory drugs (NSAIDs). Other OA patients are NSAID-insensitive and the source of their pain may stem from damage to the peripheral nervous system. This subpopulation of OA patients may respond better to neuropathic pain analgesics such as gabapentin [1]. Repicating all of these variables in a single animal model is impossible, therefore, multiple models must be considered.

Pain assessment in animal models is also complex and often open to subjective interpretation [2]. The majority of behavioural tests rely on evoked pain responses to an experimenter-applied stimulus (e.g. von Frey hairs, pressure activators). These approaches provide useful information regarding reflex mechanosensitivity with little consideration for affect. Pain tests that rely on noxious thermal stimuli have also been used to test OA pain behaviour; however, the clinical relevance of these tests is moot. Spontaneous OA pain is typically measured by gait analysis, weight bearing, grip strength, and activity levels. Since rodents are prey animals, these spontaneous behaviours are often concealed to avoid predation making their experimental quantification somewhat erratic. Electrophysiological recording of nerve activity has proven to be a powerful means of testing analgesics and unraveling neurophysiological processes in the pain pathway [3]. While these techniques give valuable, objective measures of nociception, they do not give a universal measure of pain per se.

This workshop will summarize and evaluate the various animal models of OA (chemical, surgical, spontaneous) and discuss their relative benefits for investigating OA pain. Participants will discuss how to improve the translational value of current and future preclinical models of OA pain.

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2. Malfait AM, Little CB, McDougall JJ. A commentary on modelling osteoarthritis pain in small animals. Osteoarthritis Cartilage 2013; 21: 1316-1326.
3. McDougall JJ, Andruski B, Schuelert N, Hallgrimsson B, Matyas JR. Unravelling the relationship between age, nociception and joint destruction in naturally occurring osteoarthritis of Dunkin Hartley guinea pigs. Pain 2009; 141: 222-232.

I-13
OA TRIAL BANK

S. Bierma-Zeinstra, M. van Middelkoop. *OA Trial Bank Steering Group, Univ. Med. Ctr. Rotterdam, Rotterdam, Netherlands*

Purpose: Based on small to moderate effect sizes for the wide range of symptomatic treatments in osteoarthritis (OA), and on the heterogeneity of OA patients, treatment guidelines for OA have stressed the need for research on clinical predictors of response to different treatments. Meta-analysis of individual patient data (IPD) of worldwide available RCTs would allow us to robustly identify subgroups that specifically response to certain treatment. The initiative to collect and analyze IPD in OA research is commenced by the OA Trial Bank, which is endorsed by the OARSI and the EULAR. The OA Trial Bank will bring together data from individuals with OA recruited to different clinical trials from different countries around the world to form a databank. Potential subgroups of patients for different interventions in OA patients will be predefined and will be analyzed with IPD. The procedures within the OA Trial Bank enable clinical OA researchers worldwide to initiate new research proposals and become involved in the OA Trial Bank.

Methods: This workshop will inform about the OA Trial Bank organization, its legal procedures for data transfer, and the methods used for setting the objectives and performing data analyses. Secondly, the workshop will show an example based on the first IPD analyses from randomized trials studying the effect of intra-articular glucocorticoid injections in patients with hip or knee OA. Thirdly, by means of interactive procedures, subgroup identification for other interventions will be discussed and the workshop participants will learn how they can become involved in the OA Trail Bank.